Unintended Smallpox Vaccination of HIV-1–Infected Individuals in the United States Military

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We identified 10 individuals who had undiagnosed human immunodeficiency virus type 1 (HIV-1) infection at the time of smallpox vaccination. Mean CD4 cell count was 483 cells/mm^3 (range, 286–751 cells/mm^3), and mean $\log_{10}$ plasma HIV-1 RNA load was 4.13 copies/cm^3 (range, 2.54–5.16 copies/cm^3). All vaccinees (3 primary and 7 repeat) had a normal, robust reaction without complications. Smallpox vaccine was well-tolerated in this small series of HIV-1–infected military personnel.

In 1980, the World Health Organization celebrated the eradication of smallpox (variola virus) from the globe [1]. Routine vaccination was discontinued for US military recruits in 1990, but concerns about the possible use of variola virus as an agent of bioterrorism led to the reinstitution of a US Department of Defense smallpox vaccination program in December 2002 [2].

Although smallpox vaccine is highly protective, it has well-described risks. In patients with impaired cellular immunity, there may be uncontrolled outward expansion of vaccinia infection from the primary inoculation site. This potentially fatal complication—progressive vaccinia—had an incidence of ~1 per 1 million population in a time before routine organ transplantation, cancer chemotherapy, and the advent of the AIDS epidemic [3, 4].

There are no prospective data about the safety and immunogenicity of smallpox vaccination in HIV-infected people. It is estimated that several hundred military personnel who received smallpox vaccine before the availability of an HIV serodiagnostic test were in fact infected with HIV [5, 6]. Most presumably did well, but one primary vaccinee developed progressive vaccinia and was successfully treated with vaccinia immune globulin [7]. The US military smallpox vaccination program and Centers for Disease Control and Prevention (CDC) public health guidelines currently exclude HIV-infected individuals from preemptive vaccination [2, 6]. In this report, we summarize the cases of 10 military persons who were vaccinated against smallpox in early 2003 and were later discovered to have had HIV infection at the time of vaccination.

Patients and methods. The US military smallpox vaccination program began in December 2002 and included both health care workers and operational forces deploying to southwest Asia [2]. After education about risks and benefits of smallpox vaccination, forces were screened for history of atopic dermatitis, immune suppression, pregnancy, and other contraindications to smallpox vaccine. Personnel were required to have a negative result of an up-to-date HIV test. The definition of "up-to-date" varied by branch of service but, in most cases, was required to be ⩽2 years before receipt of smallpox vaccine. Personnel with reported contraindications were not vaccinated during this predeployment vaccination program. Large-scale military mobilization occurred at a brisk pace, and many units also performed predeployment evaluations, including HIV testing, at approximately the same time as smallpox and other vaccines were given. All military vaccinees were required to return for documentation of successful vaccination on days 6–8 after vaccination. In addition, any patients ill or unable to work because of side effects from vaccination were treated by their unit's medical department.

For routine HIV screening of military personnel, blood is often saved and analyzed in batches, rather than individually with a rapid turnaround time. For example, blood specimens from the >5000 crewmembers of an aircraft carrier will often be obtained while the ship is at sea and frozen and tested weeks to months later when the ship returns to port. Positive test results are forwarded with extreme confidentiality to the individual's commanding officer and/or the specific health care

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professional who ordered the test (if performed for a clinical indication). Individuals with newly diagnosed HIV infection are notified and counseled privately about the positive test result and are then referred to one of several HIV clinical centers for evaluation, education, and treatment. Treatment is selected by the patient and physician together, in accordance with US Department of Health and Human Services guidelines [8].

Sometimes, the requirement for confidentiality results in delays in diagnosis, such as when the patient relocates or has a new commanding officer or when the health care professional who ordered the test is no longer working in the same clinic. During times of mobilization and deployment, such delays have an increased likelihood of occurring. The patients described in this paper all had positive results of HIV ELISA and Western blot tests before or within 3 weeks after smallpox vaccination, but neither the patients nor the vaccine administrators were aware of the positive test result at the time of vaccination. In most cases, the vaccinators erred by assuming that "no news was good news" when the HIV test result was not available. We included patients whose positive HIV test results were received up to 3 weeks after smallpox vaccination, because vaccinia replication and shedding occurs up to 3 weeks after vaccination, and a positive HIV serology develops at least 2–4 weeks after actual HIV infection.

Patients were identified by the HIV clinical centers, and they reported to the Military Vaccine Agency when routine review of medical history revealed recent smallpox vaccination. Laboratory studies done at the time of initial HIV evaluation included lymphocyte subset analysis by flow cytometry and measurement of plasma HIV-1 RNA levels (Amplicor ultrasensitive assay, version 1.5; Roche Molecular Systems).

Results. Between December 2002 and October 2003, >438,000 US military personnel received smallpox vaccination [2]. Among this large group of vaccinees, no cases of progressive vaccinia developed. To date, 10 of these individuals have subsequently been identified as having HIV-1 infection at the time of vaccination (table 1). All 10 patients were men. The mean age was 35.8 years (range, 21–53 years).

All 10 patients were reported to have had a major reaction (i.e., "take"), as defined by the CDC and the World Health Organization [1, 6], with no unusual side effects. Three of the 10 patients underwent primary vaccination. The remaining 7 were either known to have been vaccinated previously (all of whom would have been HIV negative at the time of primary vaccination) or were born before 1972, making it likely that they were immunized as children.

Once the HIV test results were received by their commanding officer, the patients were referred for initial HIV evaluation. By this time, the vaccination sites of the 10 patients had completely healed. At this time, 1–3 months after vaccination, the mean CD4 cell count was 483 cells/mm^3, and the mean $\log_{10}$ plasma HIV-1 RNA load was 4.13. (Laboratory data for the individual patients are shown in table 1). All patients were asymptomatic. The HIV clinical centers reported unremarkable findings of physical examinations for all patients.

Discussion. The HIV-1–infected smallpox vaccine recipients in this small series tolerated the vaccine with an appropriate reaction and no unusual sequelae. Although these data should be somewhat reassuring to public-health planners, they must be interpreted with caution because most patients were prior vaccinees, and none had AIDS at the time of vaccination. Vaccine-experienced patients may be at decreased risk for progressive complications because they may have retained some degree of cell-mediated immunity against vaccinia [5].

Other live-virus vaccines have been used safely in patients with HIV infection. Although a fatal case of pneumonia due

Table 1. Clinical characteristics of HIV-1–infected patients in the US Department of Defense smallpox vaccination program.

Patient no.	Vaccination history	CD4 cell count, cells/mm^3	CD4 cell percentage	Plasma HIV RNA load, copies/cm^3	Plasma HIV RNA load, $\log_{10}$ copies/cm^3	Response to vaccination
1	Naive	486	20	86,024	4.935	Major reaction, normal healing
2	Naive	751	41	347	2.540	Major reaction, normal healing
3	Naive	526	25	14,400	4.158	Major reaction, normal healing
4	Experienced[a]	480	41	134,682	5.129	Major reaction, normal healing
5	Experienced[a]	303	28	57,409	4.759	Major reaction, normal healing
6	Experienced[b]	514	26	1432	3.156	Major reaction, normal healing
7	Experienced	606	34	11,126	4.046	Major reaction, normal healing
8	Experienced	342	16	143,534	5.157	Major reaction, normal healing
9	Unknown	535	16	10,499	4.021	Major reaction, normal healing
10	Unknown	286	25	2699	3.431	Major reaction, normal healing
Mean overall value (±SD)	…	483 (143)	27.2 (9.1)	…	4.130 (0.890)	…

[a] Vaccinated as a child.
[b] Vaccinated in 1987.

to measles vaccination was reported in a patient with an undetectable $CD4^+$ T cell count [9], trivalent measles-mumps-rubella vaccine is routinely recommended for HIV-infected children in the United States, including those with symptomatic infection [10]. Varicella vaccine is recommended for asymptomatic HIV-infected children in the United States, [11], and yellow fever vaccine may be given to at-risk HIV-infected travelers who are not significantly immunocompromised [12].

The case of progressive vaccinia reported by Redfield et al. [7] occurred in a patient with CD4 cell counts of <25 cells/mm^3 and active cryptococcal meningitis. Similar to other live vaccines, excess risk due to vaccinia vaccination is most probable in patients with very advanced disease. The risk of complications is likely to be low for HIV-infected patients with $CD4^+$ T cell counts >200 cells/mm^3 [5, 13], such as those described in this article.

The rate of inadvertent vaccination of HIV-infected sailors and soldiers during this mass vaccination effort was very low (10 of 438,000 vaccinees). This is largely a result of the low prevalence of HIV infection in the US military, ongoing active HIV serologic screening programs, and written and verbal screening for HIV infection before smallpox vaccination. If smallpox were to be used as a biological weapon, public health officials would need to rapidly vaccinate large civilian populations, in which the potential for undiagnosed HIV infection is much greater than it is for military personnel who have undergone prior HIV screening. These unscreened populations would likely include individuals with more advanced stages of disease who would be at higher risk for complications due to smallpox vaccination.

The newly available HIV rapid tests might be used in a mass vaccination effort to quickly remove most infected individuals from the smallpox vaccination pool, but this would increase the cost and logistical complexity of such an effort. In addition, HIV-infected patients exposed to smallpox would be at high risk for death due to variola virus infection. Vaccination might be lifesaving for exposed patients with early-stage HIV infection and those receiving antiretroviral therapy. Thus, withholding vaccination from all patients with positive results of HIV rapid tests could result in increased numbers of fatalities.

Better understanding of the risks and benefits of smallpox vaccination for HIV-1–infected individuals is critically important to planning mass vaccination campaigns in urban centers after an outbreak of smallpox infection due to bioterrorism. The benign outcome associated with administration of smallpox vaccine in this small series provides support for the performance of carefully designed prospective studies of vaccinia safety and immunogenicity in healthy HIV-1–infected volunteers with normal CD4 cell counts.

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